

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Paul E. Harris and Charles Hesdorffer  
Serial No.: 09/726,883 Examiner: Gerald R. Ewoldt  
Filed : November 30, 2000 Group Art Unit: 1644  
For : GROWTH OF HUMAN DENDRITIC CELLS FOR CANCER  
IMMUNOTHERAPY IN CLOSED SYSTEM USING MICROCARRIER  
BEADS

1185 Avenue of the Americas  
New York, New York 10036  
September 19, 2002

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

INFORMATION DISCLOSURE STATEMENT

In order to ensure compliance with the applicant's duty of disclosure under 37 C.F.R. §1.56 and §1.97(a)-(d), Applicants hereby submit this Information Disclosure Statement.

Applicants direct the Examiner's attention to the following references which are listed on Form PTO-1449 attached hereto as **Exhibit A**. Copies of references 1-52 are attached hereto as **Exhibits 1-52**, respectively.

1. Schwartz-Albiez, R., et al., (1988) "The B Cell-Associated CD37 Antigen (gp40-52), Structure and Subcellular Expression of an Extensively Glycosylated Glycoprotein", Journal of Immunology, 140:905-914;
2. M. Kiremitci, et al., (1990) "Cell Adhesion to the Surfaces of Polymeric Beads", Biomater. Art. Cells Art. Org., 599-603;
3. Caux, C., et al., (1994) "Activation of human dendritic

RECEIVED

SEP 25 2002

TECH CENTER 1600/2900

cells through CD40 cross-linking", Journal of Experimental Medicine, 180:1263-1272;

4. Thomas, R., and Lipsky, P.E., (1994) "Human peripheral blood dendritic cell subsets, Isolation and characterization of precursor and mature antigen-presenting cells", Journal of Immunology, 153:4016-4028;
5. He, Y.W., et al., (1995) "Expression and function of the  $\gamma_c$  subunit of the IL-2, IL-4, and IL-7 receptors, Distinct interaction of  $\gamma_c$  in the IL-4 receptor", Journal of Immunology, 154:1596-1605;
6. Macatonia, S.E., et al., (1995) "Dendritic cells produce IL-12 and direct the development of Th1 cells from naive CD4<sup>+</sup> T cells", Journal of Immunology, 354:5071-5079;
7. Saitoh, S., et al., (1995) "Modulation of TCR-mediated signaling pathway by thymic shared antigen-1 (TSA-1)/stem cell antigen-2 (Sca-2)<sup>1</sup>", Journal of Immunology, 155:5574-5581;
8. Bender, A., et al., (1996) "Improved methods for the generation of dendritic cells from nonproliferating progenitors in human blood", Journal of Immunological Methods, 196, 121-135.
9. Cella, M., et al., (1996) "Ligation of CD40 on dendritic cells triggers production of high levels of interleukin-12 and enhances Tcell stimulatory capacity: T-T help via APC activation", Journal of Experimental Medicine, 184: 747-752.

10. Romani, N., et al., (1996) "Generation of mature dendritic cells from human blood, An improved method with special regard to clinical applicability", Journal of Immunological Methods, 396:137-151;
11. Zhou, L.J. and Tedder, T.F., (1996) "CD14<sup>+</sup> blood monocytes can differentiate into functionally mature CD83<sup>+</sup> dendritic cells", Proc. Natl. Acad. Sci. USA, 93:2588-2592;
12. Kalinski, P., et al., (1997) "IL-12-deficient dendritic cells, generated in the presence of prostaglandin E<sub>2</sub>, promote type 2 cytokine production in maturing human naive T helper cells<sup>1</sup>", Journal of Immunology, 159:28-35;
13. Schuler, G. and Steinman R.M. (1997) "Dendritic cells as adjuvants for immune-mediated resistance to tumors", J. Exp. Med., 186:1183-1187;
14. Takahashi, K., et al., (1997) "Dendritic cells generated from human blood in granulocyte macrophage-colony stimulating factor and interleukin-7", Human Immunology, 55:103-116;
15. Bartholeyns, J., et al., (1998) "Cellular Vaccines", Res. Immunol., 149:647-649;
16. Bonecchi, R., et al., (1998) "Differential expression of chemokine receptors and chemotactic responsiveness of type 1 T helper cells (Th1s) and Th2s", Journal of Experimental Medicine, 187:129-134;

17. Di Nicola, M., (1998) "Human dendritic cells: natural adjuvants in antitumor immunotherapy", Cytokines, Cellular & Molecular Therapy, 265-273;
18. Eisen, M.B., et al., (1998) "Cluster analysis and display of genome-wide expression patterns", Proceedings of the National Academy of Sciences of the United States of America, 95:14863-14868;
19. Escola, J.M., et al., (1998) "Selective enrichment of tetraspan proteins on the internal vesicles of multivesicular endosomes and on exosomes secreted by human B-lymphocytes", Journal of Biological Chemistry, 273:20121-20127;
20. Ferrer, M., et al., (1998) "Pattern of expression of tetraspanin antigen genes in Burkitt lymphoma cell lines", Clinical and Experimental Immunology, 113:346-352;
21. Legler, D.F., et al., (1998) "B cell-attracting chemokine 1, a human CXC chemokine expressed in lymphoid tissues, selectively attracts B lymphocytes via BLR1/CXCR5", Journal of Experimental Medicine, 187:655-660.
22. Mellman, I., et al., (1998) "Antigen processing for amateurs and professionals", Trends in Cell Biology, 8:231-237;
23. Ria, F., et al., (1998) "Th1 cells induce and Th2 inhibit antigen-dependent IL-12 secretion by dendritic cells", European Journal of Immunology, 28:2003-2016;

24. Sparwasser, T., et al., (1998) "Bacterial DNA and immunostimulatory CpG oligonucleotides trigger maturation and activation of murine dendritic cells", European Journal of Immunology, 28:2045-2054;
25. Dhodapkar, M.V., et al., (1999) "Rapid generation of broad T-cell immunity in humans after a single injection of mature dendritic cells", Journal of Clinical Investigation, 104:173-180.
26. Glaser, A., et al., (1999) "Collection of mononuclear cells in the Spectra for the generation of dendritic cells", Transfusion, 39:661-662;
27. Hartmann, G., et al., (1999) "CpG DNA: a potent signal for growth, activation, and maturation of human dendritic cells", Proceedings of the National Academy of Sciences of the United States of America, 96:9305-9310;
28. Kalinski, P., et al., (1999) "T-cell priming by type-1 and type-2 polarized dendritic cells: the concept of a third signal", Immunology Today, 20:561-567;
29. Kapsenberg, M.L. and Kalinski, P., (1999) "The concept of type 1 and type 2 antigen-presenting cells", Immunology Letters, 69:5-6;
30. Papadopoulos, E.J., et al., (1999) "Fractalkine, a CX3C chemokine, is expressed by dendritic cells and is up-regulated upon dendritic cell maturation", European Journal of Immunology, 29:2551-2559;

31. Randolph, D.A., (1999) "The role of CCR7 in T<sub>H</sub>1 and T<sub>H</sub>2 cell localization and delivery of B cell help in vivo", Science, 286:2159-2162;
32. Rescigno, M., et al., (1999) "Coordinated events during bacteria-induced DC maturation", Immunology Today, 20:200-203;
33. Sallusto, E., et al., (1999) "Distinct patterns and kinetics of chemokine production regulate dendritic cell function", European Journal of Immunology, 29:1617-1625;
34. Sallusto, F., et al., (1999) "Two subsets of memory T lymphocytes with distinct homing potentials and effector functions", Nature, 401:708-712;
35. Thurner, B., et al., (1999) "Generation of large numbers of fully mature and stable dendritic cells from leukapheresis products for clinical application", Journal of Immunological Methods, 223:1-15;
36. Ansel, K.M., et al., (2000) "A chemokine-driven positive feedback loop organizes lymphoid follicles," Nature, 406:309-314;
37. Banchereau, J., et al., (2000) "Immunobiology of dendritic cells", Annual Review of Immunology, 18:767-811;
38. Bertho, N., et al., (2000) "HLA-DR-mediated apoptosis susceptibility discriminates differentiation stages of dendritic/monocytic APC<sup>1</sup>", Journal of Immunology,

164:2379-2385;

39. Dhodapkar, M.V., et al., (2000) Mature dendritic cells boost functionally superior CD8<sup>+</sup> T-cell in humans without foreign helper epitopes", Journal of Clinical Investigation, 105:R9-R14;
40. Hashimoto, S.I., et al., (2000) "Identification of genes specifically expressed in human activated and mature dendritic cells through serial analysis of gene expression", Blood, 96:2206-2214;
41. Ishii, M., et al., (2000) "Direct comparison of GeneChip and SAGE on the quantitative accuracy in transcript profiling analysis", Genomics, 68:136-143;
42. Knobeloch, K.P., et al., (2000) "Targeted inactivation of the tetraspanin CD37 impairs T-cell-dependent B-cell response under suboptimal costimulatory conditions", Molecular and Cellular Biology, 20:5363-5369;
43. Kodaira, Y., et al., (2000) "Phenotypic and functional maturation of dendritic cells mediated by heparan sulfate<sup>1</sup>", Journal of Immunology, 165:1599-1604;
44. Langenkamp, A., et al., (2000) "Kinetics of dendritic cell activation: impact on priming of TH1, TH2 and nonpolarized Tcells", Nature Immunology, 1:311-316;
45. Larsson, M., et al., (2000) "Requirement of mature dendritic cells for efficient activation of influenza A-specific memory CD8<sup>+</sup> T cells<sup>1</sup>", Journal of Immunology,

165:1182-1190;

46. Li, L., et al., (2000) "Effect of interleukin-7 on the in vitro development and maturation of monocyte derived human dendritic cells", Scandinavian Journal of Immunology, 51:361-371.
47. Maffei, A., et al., (2000) "A novel closed system utilizing styrene copolymer bead adherence for the production of human dendritic cells", Transfusion, 40:1419-1420;
48. Neumann, M., et al., (2000) "Differential expression of Rel/NF- $\kappa$ B and octamer factors is a hallmark of the generation and maturation of dendritic cells", Blood, 95:277-285;
49. Tanaka, H., et al., (2000) "Human monocyte-derived dendritic cells induce naive T cell differentiation into T helper cell type 2 (Th2) or Th1/Th2 effectors: Role of stimulator/responder ratio", Journal of Experimental Medicine, 192, 405-412;
50. Tjoa, B.A. and Murphy, G.P., (2000) Development of dendritic-cell based prostate cancer vaccine", Immunology Letters, 74:87-93;
51. Vieira, P.L., et al., (2000) "Development of Th1-inducing capacity in myeloid dendritic cells requires environmental instruction<sup>1</sup>", Journal of Immunology, 164:4507-4512;



52. Ebner, S., et al., (2001) "Production of IL-12 by human monocyte-derived dendritic cells is optimal when the stimulus is given at the onset of maturation, and is further enhanced by IL-4<sup>1</sup>", Journal of Immunology, 166:633-641;

Copies of the following references (53-72) will be submitted to the U.S. Patent and Trademark Office after Applicants obtain copies thereof.

53. Boyum, A., (1983) "Isolation of human blood monocytes with Nycodenz, a new non-ionic iodinated gradient medium", Scandinavian Journal of Immunology, 17:429-436;
54. Sallusto, F. and Lanzavecchia, A., (1994) "Efficient presentation of soluble antigen by cultured human dendritic cells is maintained by granulocyte/macrophage colony-stimulating factor plus interleukin 4 and downregulated by tumor necrosis factor alpha", Journal of Experimental Medicine, 179:1109-1118;
55. Bernhard, H., et al., (1995) "Generation of immunostimulatory dendritic cells from human CD34+ hematopoietic progenitor cells of the bone marrow and peripheral blood", Cancer Research, 55:1099-1104;
56. Koch, E., et al. (1995) "Antigen processing in populations of mature murine dendritic cells is caused by subsets of incompletely matured cells", Journal of Immunology, 155:93-100;
57. Sallusto, E., (1995) "Dendritic cells use

macropinocytosis and the mannose receptor to concentrate macromolecules in the major histocompatibility complex class II compartment: downregulation by cytokines and bacterial products", Journal of Experimental Medicine, 182:389-400;

58. Siena, S., et al. (1995) "Massive ex vivo generation of functional dendritic cells from mobilized CD34+ blood progenitors for anticancer therapy", Experimental Hematology, 23:1463-1471;
59. Grass, H.J., (1996) "Molecular, structural, and biological characteristics of the tumor necrosis factor ligand superfamily", International Journal of Clinical and Laboratory Research, 26:143-159;
60. Lin, E.Y., et al., (1996) "A1, a Bcl-2 family member, prolongs cell survival and permits myeloid differentiation", Blood, 87:983-992;
61. Ye, Z., (1996) "In vitro expansion and characterization of dendritic cells derived from human bone marrow CD34+ cells", Bone Marrow Transplantation, 18:997-1008;
62. Kalinski, P., (1997) "Dendritic cells, obtained from peripheral blood precursors in the presence of PGE2, promote Th2 responses", Advances in Experimental Medicine and Biology, 417:363-367;
63. Morse, M.A., et al., (1997) "Generation of dendritic cells in vitro from peripheral blood mononuclear cells with granulocyte-macrophage-colony-stimulating factor,

interleukin-4, and tumor necrosis factor-alpha for use in cancer immunotherapy", Annals of Surgery, 226:6-16.

64. Sallusto, E., et al., (1998) "Rapid and coordinated switch in chemokine receptor expression during dendritic cell maturation", European Journal of Immunology, 28:2760-2769;
65. Zitvogel, L., et al., (1998) "Eradication of established murine tumors using a novel cell-free vaccine: dendritic cell-derived exosomes", Nature Medicine, 4:594-600;
66. Gattei, V., et al. (1999) "CD30 ligand (CD30L)-expressing acute myeloid leukemias: a new model of paracrine interactions for the regulation of blast cells proliferation", Leukemia and Lymphoma, 35:21-35;
67. Granucci, F., et al., (1999) "Early events in dendritic cell maturation induced by LPS", Microbes and Infection, 1:1079-1084;
68. Hashimoto, S., et al., (1999) "Serial analysis of gene expression in human monocyte-derived dendritic cells", Blood, 94:845-852;
69. Lanzavecchia, A., (1999) "Dendritic cell maturation and generation of immune responses", Haematologica, 84:23-25;
70. Brinckerhoff, L.H., et al., (2000) "Melanoma vaccines", Current Opinion in Oncology, 12:163-173;
71. Rieser, C., et al., (2000) "Mature dendritic cells induce

Paul E. Harris and Charles Hesdorffer  
Serial No.: 09/726,883  
Filed: November 30, 2000  
Page 12

T-helper type-1-dominant immune responses in patients with metastatic renal cell carcinoma", Urologia Internationalis, 63:151-159; and

72. Toney, L.M., et al., (2000) "BCL-6 regulate chemokine gene transcription in macrophages", Nature Immunology, 3:214-220.

A non-final Office Action was issued July 15, 2002 by the Patent Office in connection with the subject application. A response to the July 15, 2002 Office Action has not yet been filed.

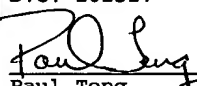
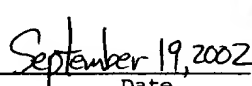
This Information Disclosure Statement is filed pursuant to 37 C.F.R. §1.97(c)(2), after the mailing date of a first Office Action, but before a Final Office Action, a Notice of Allowance, or an action that otherwise closes prosecution in the application. The fee under 37 C.F.R. §1.17(p) for filing an Information Disclosure Statement pursuant to 37 C.F.R. §1.97(c)(2) is ONE HUNDRED AND EIGHTY DOLLARS (\$180.00) and a check in that amount is enclosed.

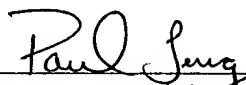
If a telephone conference would be of assistance in advancing the prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

Paul E. Harris and Charles Hesdorffer  
Serial No.: 09/726,883  
Filed: November 30, 2000  
Page 13

No fee, other than the enclosed \$180.00 fee under 37 C.F.R. §1.17(p), is believed to be due in connection with the filing of this Information Disclosure Statement. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.	
 Paul Teng Reg. No. 40,837	 September 19, 2002 Date

  
John P. White  
Registration No. 28,678  
Paul Teng  
Registration No. 40,837  
Attorneys for Applicants  
Cooper & Dunham, LLP  
1185 Avenue of the Americas  
New York, New York 10036  
(212) 278-0400